REMARKS

Claims 1-14 and 43-66 are pending in the application. Claims 44-49 are allowed and claims 1-14, 43 and 60-66 are rejected.

Claims 1, 8, 11 and 14 have been amended, claims 12, 13, 60 and 64-66 have been cancelled without prejudice or disclaimer, and claims 67 and 68 have been added. Accordingly, claims 1-11, 14, 43-59, 61-63, 67 and 68 will be pending in the application upon entry of the amendments presented herein.

Claim 1 has been amended to recite that the wild type receptor is selected from the group consisting of the chemokine α family of receptors. Support for the amendment to claim1 can be found at least, for example, in the specification at page 2, line 18 through page 3, line 6. Claims 8, 11 and 14 were amended to correct typographical omissions. Claims 67 and 68 have been added to claim more fully the invention. Support for the addition of claims 67 can be found at least, for example, in the specification at page 20, lines 8-13. Support for the addition of claim 68 can found at least, for example, in the specification at page 2, lines 18-31, Table 1 and page 3, lines 5-6. No new matter has been added.

Any amendment to and/or cancellation of the claims should in no way be construed as acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this application or in one or more separate applications.

Applicants note with appreciation the withdrawal of the rejection under 35 U.S.C. §112, second paragraph and allowance of claims 44-59.

Rejection of Claims Under 35 U.S.C. §112, First Paragraph

Claims 1-14, 43 and 60-66 are rejected under 35 U.S.C. §112, first paragraph, "because the specification, while being enabling for a mutant IL8 receptor and a mutant galanin receptor, does not reasonably provide enablement for any other mutant mammalian G protein coupled receptor." The Office Action, at page 2, indicates that "[t]here is not adequate guidance as to the

nature of the mutant mammalian G protein coupled receptor which Applicants claim." The Office Action further indicates that "[t]he specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with this claim." The Examiner indicates that claims 1-14 and 43 as written encompass mutants of any and all GPCRs, and that claims 60-66 encompass six groups of receptors, although only the IL8A and human galanin I receptors are the only two that are enabled. Therefore, the Examiner has maintained the rejection of these claims, but has allowed claims 44-59 because these claims are directed to the IL8A and human galanin I mutant receptors.

Claims 12, 13, 60 and 64-66 have been cancelled without prejudice or disclaimer. Therefore, the rejection is moot as to those claims. Applicants respectfully traverse the rejection of claims 1-11, 14, 43, 50-59, 61-63 and 67 for the reasons of record set forth in the responses filed November 2, 2003 and December 18, 2002, and again assert those reasons herein.

Applicants further traverse the rejection for the additional reasons set forth below. At the outset, Applicants note that claim 1 has been amended to recite mutants of wild type GPCRs selected from the chemokine α family of receptors. Thus, claims 1-11, 14, 43, 50-59, 61-63 and 67 are no longer directed to of any and all GPCRs, but rather to a discreet group of receptors, namely the chemokine α family of receptors.

Although the Examiner relies on the Gether reference for teaching that the GPCR superfamily is large and diverse and that residues necessary for function are not shared between families, Applicants again point out that the Gether reference teaches that ***"[s]ignificant sequence homology is found, however, within several subfamilies"*** (page 91). As taught by Gether, chemokines are one of six subgroups belonging to subfamily A of the superfamily of GPCRs. (See the Gether reference, page 91-92 and Figure 1). Gether further teaches that subfamily A receptors are characterized by a series of highly conserved key residues; most subfamily A receptors have a disulfide bridge that connects the second and third extracellular loop; and the majority of subfamily A receptors have a palmitoylated cysteine in the carboxy-terminal tail causing formation of a putative fourth intracellular loop. In view of the teachings of Gether, one of ordinary skill in the art would expect subfamily A receptors to behave in the same

way when a mutation is introduced into the amino acid motif ($X_1X_2X_3X_4$) closer to the C-terminal end than the N-terminal end.

Receptors of the chemokine α family represent a subset within the chemokine receptors. The instant specification teaches that members of the chemokine α subset are so classified based on their gene cluster on chromosome 4 (q12-21) and the fact that the first two of their four cysteine groups are separated by one amino acid (C-X-C) (specification, page 2, lines 18-31 and Table 1). Receptors of the chemokine α subset include, *e.g.*, receptors for IL-8, melanoma growth-stimulating activity (MGSA/GRO), platelet factor 4 (PF-4), β-thromboglobulin (βTG), IP-10, and ENA-78 (specification, page 3, lines 5-6).

Based on the teachings of Gether, in conjunction with the teachings of the specification, one of ordinary skill in the art would expect mutants of receptors within the chemokine α family of receptors to have enhanced ligand-binding problems. Indeed, this is shown in the working example for the IL8A receptor, a representative member of the chemokine α family.

Applicants have provided working examples that disclose how to make and express GPCRs of the instant invention, and have specifically shown that the mutant GPCRs do in fact generate a greater signal than that generated by the wild-type receptor. In this regard, the Examiner's attention is invited to Example 2, page 65, line 36 through page 66, line 10. In particular, Example 3 details the generation of a mutant galanin receptor-1 (GalR1) based upon a mutation that was shown to increase IL-8A receptor signaling (page 67, lines 10-48 of the specification). The mutation that increased the IL-8A receptor response to ligand similarly caused an increased response to ligand in the Ga1R1 as well.

In short, the working examples of the present invention demonstrate a correlation between the function of GPCRs, *i.e.*, enhanced signaling, and specific amino acids within the $X_1X_2X_3X_4$ motif. Applicants have clearly identified this motif, provided the location of this motif in the protein, and also provided the candidate amino acids for this motif. In addition, Applicants have actually demonstrated increased signaling by the mutant receptor as compared to the wild-type receptor.

As the level of skill in the art is high, Applicants submit that one of ordinary skill in the art would be able to make and use the invention commensurate in scope with the amended claims

presented herein, using nothing more that routine experimentation, given the teachings of the application and working Examples 1 and 2 directed to the mutant IL8A receptor.

The Examiner also relies on three other references, Bowie *et al.*, Yan *et al.*, and Voet *et al.*, to support his position that the protein art is unpredictable. In particular, the Office Action at page 3 states that the unpredictability of the protein art is shown in Bowie *et al.* (*Science*, 1990, 247:1306 – 1310), which teaches that certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions, and that utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. The Office Action also indicates that the in certain cases, a change of only two-amino acid residues in a protein results in switching of the binding of the protein from one receptor to another (Yan *et al.* (*Science*, 2000, 290:523-527). Furthermore, at pages 3-4, the Office Action indicates that it is also known in the art that a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell, as exemplified in Voet *et al.* (1990), which teaches that a single Glu to Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, column 2, first paragraph) (see pages 3-4 of the Office Action).

However, none of these references is directed to GPCRs. Bowie *et al.* provide a general review of the effect of amino acid substitutions in proteins in general. There is no mention of GPCRs. Yan *et al.* are concerned with the X-linked ectodysplasin-A2 receptor (XEDAR), which has a single transmembrane region. A receptor such as XEDAR is much different than a GPCR, let alone a cytokine receptor within subfamily A of the GPCR superfamily. Likewise, Voet *et al.* are concerned with amino acid substitutions in the hemoglobin protein. The proteins described in these references are so different from GPCRs that one of ordinary skill in the art would not find their teachings as dispositive of the behavior of GPCRs, especially chemokines.

Moreover, Applicants note that the publication date of the Bowie and Voet references is 1990. This date is 8 years before the July 28, 1998 priority date of the instant application. Given the rapid changes in technology that occur in this particular field, the Bowie and Voet and

references may not necessarily be considered state of the art at the time the instant application was filed. Indeed, although examples exist of polypeptide families wherein individual members have distinct, even opposite, biological activities, growing databases and improved search techniques, particularly the iterated PSI-BLAST tool, have yielded substantial improvement in secondary structure prediction accuracy. According to Rost, a copy of which was made of record with the response filed December 18, 2002, "[s]econdary structure predictions are increasingly becoming the work horse for numerous methods aimed at predicting protein structure and function." Burkhard Rost, *Review: Protein Secondary Structure prediction Continues to Rise* (2001) J. Structural Biology 134: 204-218. Furthermore, neither of these references is directed to GPCRs.

Thus, Applicants respectfully submit that, although some references may critique the usefulness of approaches that predict protein function based on protein homology, the truth is that during the genomic era, prediction of protein function based on protein homology was successfully achieved in a plethora of newly cloned molecules, including a plethora of newly cloned molecules that are the subject of multiple issued patents. Moreover, the Gether reference indicates that the subfamily A of GPCRs is the most studied (page 91, right column, third paragraph) and, in particular, the binding sites for endogenous ligands in subfamily A receptors are the most well characterized (page 95, right column, first full paragraph).

In summary, it is irrelevant that some isolated references that are not directed specifically to GPCRs (such as the references cited by the Examiner) question the usefulness of the structure/function-based approach, because Applicants have successfully used this approach to predict the biological activity of the molecules of the present invention.

Rejection of Claims Under 35 U.S.C. §112, First Paragraph

Claims 1-14, 43 and 60-66 are rejected under 35 U.S.C. §112, first paragraph, "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was field, had possession of the claimed invention."

Claims 12, 13, 60 and 64-66 have been cancelled without prejudice or disclaimer. Therefore, the rejection is moot as to those claims. Applicants respectfully traverse the rejection

of claims 1-11, 14, 43, 50-59 and 61-63 for the reasons of record set forth in the responses filed November 2, 2003 and December 18, 2002, and again assert those reasons herein. Applicants further traverse the rejection for the additional reasons set forth below.

At the outset, Applicants note that claim 1 has been amended to recite mutants of wild type GPCRs selected from the chemokine α family of receptors. Thus, claims 1-11, 14, 43, 50-59 and 61-63 are no longer directed to of any and all GPCRs, but rather to a discreet group of receptors, namely the chemokine α family of receptors.

Applicants respectfully submit that there is sufficient written description in Applicants' specification regarding the claimed molecules, to inform a skilled artisan that Applicants were in possession of the claimed invention at the time the application was filed, as required by section 112, first paragraph (see M.P.E.P. §2163.02).

For reasons discussed in detail below, the instant specification satisfies this requirement for the claimed invention. It is Applicants' position that the claimed genus of the mutant GPCRs of the present invention is defined by structural features that are described in the specification, recited in the claims, and commonly possessed by its members. In particular, the structure of the claimed genus is taught in the specification, *i.e.*, the structure of the mutant GPCR, the corresponding the amino acid motif [$X_1X_2X_3X_4$] and the position of the point mutation within the amino acid motifs (see page 7, line 17 through page 8, line 40 of the specification). Furthermore, this structure was already well-know in the art through such publications as, for example, Navarro *et al.* WO/92/18641.

In addition, the structural features, active domains, binding regions and other features that are common to GPCRs in general and the chemokine receptors of subfamily A were well known to those of ordinary skill in the art at the time the application was filed. Indeed, this is acknowledged in the Gether reference. Furthermore, a specific subset of chemokine receptors, *i.e.*, the chemokine α family receptors, is fully described in the instant specification at page 2, lines 18-31, Table 1 and page 3, lines 5-6.

Contrary to the Examiner's assertion, Applicants respectfully submit that the instant specification teaches distinguishing structural features within the claimed genus. For example, the instant specification discloses the amino acid sequence of the rabbit IL8A receptor showing putative membrane spanning domains, *e.g.*, Arg73 (1st intracellular loop), Met246 (3rd

intracellular loop) and Gly320 (C-terminal tail) (see page 10, lines 19-21 of the specification. Moreover, G-protein coupled receptors of the subfamily A are known molecules with a conserved structure as taught by Gether.

In summary, Applicants have described a genus of mutant GPCRs based on structural features that are common to a substantial portion of the genus and have provided within the instant specification the amino acid motifs and the point mutations within the amino acid motif that possess these features. Accordingly, Applicants submit that the present invention satisfies the requirements of 35 U.S.C. §112, first paragraph.

CONCLUSION

Reconsideration and withdrawal of the remaining rejections and allowance of all the pending claims are respectfully requested. If a telephone conversation with Applicants' Attorney would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at the telephone number indicated below.

Respectfully submitted,
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